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ARTICLE

Model-informed pediatric dose selection of marzeptacog alfa (activated): An exposure matching strategy

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Abstract

Marzeptacog alfa (activated) (MarzAA) is an activated recombinant human rFVII variant intended for subcutaneous (s.c.) administration to treat or prevent bleeding in individuals with hemophilia A (HA) or B (HB) with inhibitors, and other rare bleeding disorders. The s.c. administration provides benefits over i.v. injections. The objective of the study was to support the first-in-pediatric dose selection for s.c. MarzAA to treat episodic bleeding episodes in children up through 11 years in a registrational phase III trial. Assuming the same exposure-response relationship as in adults, an exposure matching strategy was used with a population pharmacokinetics model. A sensitivity analysis evaluating the impact of doubling in absorption rate and age-dependent allometric exponents on dose selection was performed. Subsequently, the probability of trial success, defined as the number of successful trials for a given pediatric dose divided by the number of simulated trials ($n = 1000$) was studied. A successful trial was defined as outcome where four, three, or two out of 24 pediatric subjects per trial were allowed to fall outside the adult exposures after s.c. administration of 60 μg/kg. A dose of 60 μg/kg in children with HA/HB was supported by the clinical trial simulations to match exposures in adults. The sensitivity analyses further supported selection of the 60 μg/kg dose level in all age groups. Moreover, the probability of trial success evaluations given a plausible design confirmed the potential of a 60 μg/kg dose level. Taken together, this work demonstrates the utility of model-informed drug development and could be helpful for other pediatric development programs for rare diseases.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

There is currently no s.c. administered alternative for the treatment of episodic bleeding. Rare disease drug development programs suffer from small sample size, making it hard to follow the traditional developmental pathway.

WHAT QUESTION DID THIS STUDY ADDRESS?

Using an adult population pharmacokinetic model coupled with an exposure matching strategy and sensitivity analysis, clinical trial simulations of different doses in pediatric patients were performed to find a dose that matches exposures in adults.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

A model-based rationale was developed for dose selection in pediatric phase III trials against hemophilia A/hemophilia B with inhibitors. The approach exemplifies how adult data can inform first-in-pediatric dose selection for a registrational phase III trial.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The framework demonstrates how drug development in children for a rare disease may benefit from a pharmacokinetic run-in phase prior to an efficacy evaluation to confirm dose selection, a strategy that can inform other rare disease drug development programs.

INTRODUCTION

Congenital hemophilia A (HA) and hemophilia B (HB) are rare, sex-linked chromosomal recessive bleeding disorders caused by functional deficiency of coagulation factors VIII (FVIII) or IX (FIX), respectively. These deficiencies may lead to unusual spontaneous and/or trauma-related bleeding.[1,2] Children may experience the first bleeding episodes at a young age, usually around the time where they start to move around. If untreated, bleeding can be associated with significant comorbidities, such as crippling arthropathy, with significant negative effects on the child's and his family's quality of life. First-line therapy is replacement with the missing factor. However, for approximately a third of individuals with HA and a smaller fraction of individuals with HB, their disease is complicated by the development of inhibitors. The inhibitors are alloantibodies which form against the infused replacement therapy and render it inactive. The current standard of care for acute breakthrough bleeding events in patients with inhibitor-complicated HA/HB are intravenously (i.v.) administered replacements, such as wild-type recombinant activated coagulation factor VII (rFVIIa)[3] or other bypassing products. The time required to prepare and administer drugs by i.v. infusion, together with risk of infections and associated pain, has been known to negatively impact treatment compliance.[4,5] In addition, failure to achieve good, fast, and repeated i.v. access is a limiting factor that lowers therapy adherence.[6] Moreover, the short 2.3-h half-life of approved rFVIIa often requires repeat administration every 2 to 3 h to control hemorrhage. Due to the high initial peak concentrations following i.v. infusion, there is a risk for thrombosis, which is the most common adverse event in treatment with rFVIIa.[7]

In comparison with i.v. infusion, subcutaneous (s.c.) administration introduces major advantages. The s.c. administration can more easily be completed under typical work/life circumstances, for example, at school or at sports or social events. It is faster to dose via s.c. injection compared to i.v. infusions, and this route of administration may improve or maintain efficacy that is much less disruptive to the individuals needing treatment. Previous studies have indicated a clear patient preference for s.c. administration, and the main reasons were time-saving and the ability to dose outside treatment centers.[5] As the standard-of-care alternatives have limitations leading to suboptimal adherence and efficacy, novel improved biotherapeutics are needed to satisfy an unmet medical need in children as well as adults with HA/HB with inhibitors, as well as other rare bleeding disorders, such as FVII deficiency and Glanzmann thrombasthenia. Marzeptacog alfa (activated; MarzAA) is a novel s.c. administered rFVIIa variant with increased bioavailability, higher potency, and prolonged half-life compared to wild-type rFVIIa.[8,9] It has been studied in adults,[8,9] with meaningful clinical and statistical efficacy demonstrated in a prophylactic setting.[9] In a subsequent phase III pivotal trial[10] in adults, an s.c. dose of 60 μg/kg was shown to have potential to treat bleeding episodes safely and effectively,[10] although the trial was terminated early due reasons other than efficacy and safety.

A general recommendation by regulatory agencies is to submit a pediatric study plan (US Food and Drug Administration [FDA])[11] and/or a pediatric investigation plan (European Medicines Agency [EMA]),[12] shortly after the end of a phase II meeting or the first-in-human pharmacokinetic (PK) study, respectively. The plan should include study designs, end points (PK,

pharmacodynamic [PD], and PK/PD), and statistical analysis of future pediatric studies. A modeling and simulation strategy is encouraged to support study design/analysis and dose selection. Based on adult data in early clinical trials, model-based methods are suggested to inform first-in-pediatric dose selection.[13,14] In children, and in particular for children above 2 years of age, fixed exponents (0.75 and 1 for clearance [CL] and volume of distribution [V] terms, respectively)[13,14] can often be used for a description of the PKs.[15] In younger children, the general recommendation is to account for maturation to describe physiological development of elimination pathways.[16–19] However, in the absence of data to account for ontogeny, different approaches have been described in the literature to reduce bias and make more informed first-in-pediatric dose selection.[17,20] For coagulation FVIII and FIX, allometry with fixed exponents has previously been demonstrated to provide good prediction of drug CL down to 5 years of age.[18] However, in smaller children and in particular children less than 2 years of age, the performance of a fixed exponent is unclear,[18] in particular for therapeutic proteins. The age-dependent exponent (ADE) method has been suggested to reduce the risk of overpredicting CL in children less than 2 years of age, and has been considered suitable for first-in-pediatric dose selection of coagulation factors, and other non-antibody proteins.[18,19] Although helpful, these methods are not intended to replace but rather to make an informed decision on dosing at the initiation of a pediatric trial.

Using modeling and simulations,[18,19,21,22] this work aimed to inform the dose selection in an eventual pediatric phase III trial studying the efficacy and safety of s.c. MarzAA for on-demand treatment, and control of spontaneous or traumatic bleeding episodes in children with HA/HB with inhibitors.

METHODS

A previously developed adult population PK model was used[23] in this work (Table S1). The model was a two-compartment model with estimated baseline endogenous FVIIa. The s.c. absorption was described by zero order input into an absorption compartment, and first order absorption and elimination. Allometric scaling was used on all CL and V parameters with fixed exponents of 0.75 and 1, respectively. Interindividual variability (IIV) was included in CL and central Vc with covariance between the CL and Vc IIV terms, and in baseline FVIIa, bioavailability, and absorption rate. Interoccasional variability was included on the zero-order input to the absorption compartment. The residual unexplained variability was described by a proportional model. the relationship between CL and bodyweight (BW) and BW normalized CL versus plausible BW values were studied on a typical level, to visualize the implications of extrapolation below 2 years of age using only allometric scaling with fixed exponents.

For all simulations in children, the National Health and Nutrition Examination Survey (NHANES) dataset of the US Centers for Disease Control and Prevention[24] was used as the source for randomly sampled pediatric covariates. Demographic data, such as age, sex, and BW were collected from the 1999 to 2018 NHANES databases. Female subjects and subjects 12 years and older were excluded according to the inclusion criteria for the pediatric trial. For each age in months, a distribution of BW was constructed. BW values outside the 97.5th and 2.5th percentiles were considered outliers and removed. Only age and BW were used for further analyses.

Exposure-matching clinical trial simulations to inform dose selection

Individual concentration-time profiles with rich sampling were simulated in 1000 male subjects per age group (0.5, 1, 2, 4, 6, and 11 years) following 60 to 120 (increments of 15) μg/kg given either as a single dose, two doses 3 h apart, or three doses 3 h apart (Table 1). The dose levels were chosen based on clinical experience and considering pharmaceutical development constraints. Based on the simulated profiles in pediatric subjects, median and 95% prediction intervals (PI) of area under the concentration curve over 24 h ($AUC_{0\text{-}24h}$) and maximum concentrations over 24 h ($C_{max(0\text{-}24h)}$) were derived for each dose and age group. The course of disease and effects of drug were expected to be sufficiently similar in adults and pediatric subjects. In addition, current bypassing therapies are dosed independent of age, but rather based on BW.[25] As 60 μg/kg was selected as the phase III dose in adults,[10] a matching strategy was used in which the model predicted 95% PI of $AUC_{0\text{-}24h}$ and $C_{max(0\text{-}24h)}$ from adults following 60 μg/kg given once, two times or three times (both three hourly intervals) were used as the matching range.

Sensitivity analysis

Allometry was only used in disposition parameters and the simulations assumed that absorption processes were similar between adults and children. To test that assumption, a sensitivity analysis was performed to study the influence of absorption differences between adult and pediatric subjects on the exposure matching results. Based

Dose (μg/kg)	Dosing interval	Age groups (years)[a]
60	Single dose, two doses 3 h apart or three doses 3 h apart	11, 6, 4, 2, 0.5
60	Single dose	<2, 2 to <6, and 6–11[b]
75	Single dose, two doses 3 h apart or three doses 3 h apart	11, 6, 4, 2, 0.5
90	Single dose, two doses 3 h apart or three doses 3 h apart	11, 6, 4, 2, 0.5
105	Single dose, two doses 3 h apart or three doses 3 h apart	11, 6, 4, 2, 0.5
120	Single dose, two doses 3 h apart or three doses 3 h apart	11, 6, 4, 2, 0.5

TABLE 1 Dose levels, frequency of administration, number of children, and age groups used in all clinical trial simulations for prediction of $AUC_{0\text{-}24\,h}$ and $C_{max(0\text{-}24\,h)}$.

Abbreviations: $AUC_{0\text{-}24h}$, area under the concentration curve over 24 h; $C_{max(0\text{-}24h)}$, maximum concentrations over 24 h.

[a] $n = 1000$ per each age group.

[b] Two, 10, and 12 pediatric patients in age subgroups <2, 2 to <6, and 6 to 11, respectively.

on previously found differences in absorption for biologics,[26,27] a scenario of doubling the absorption constant in pediatric subjects was studied for dose levels 60, 90, and 120 μg/kg (single dose). The three dose levels were chosen as they have also been previously studied in adults.[23]

Due to the absence of quantitative maturation functions for FVIIa and uncertainty associated with using fixed exponents, a sensitivity analysis was performed, in which the ADE allometric model[17–19] was applied and compared with using fixed allometric exponents of 0.75 and 1 for CL and V terms, to study impact on dose selection. In this approach, a fixed exponent of 0.75 was applied for 11 and 6-year-old groups, whereas an exponent of 0.9 was applied for the 4-year-old group. For the younger children in the 2, 1, and 0.5-year-old groups, an exponent of 1 was used.

Probability of trial success

Probability of trial success was studied using clinical trial simulations and was defined as the number of successful trials divided by total number of trials. One thousand clinical trials were simulated with 24 pediatric subjects in each trial following a single s.c. dose (60 μg/kg). The 24 subjects in each of the 1000 trials were divided as two, 10, and 12 children in age subgroups less than 2, 2 to less than 6, and 6 to 11 years, respectively (Table 1). The allocation and number of subjects in the design described here was considered plausible given the rarity of the disease, and a similar design has been used for pediatric trials studying another i.v. rFVIIa drug.[28] PK concentrations were simulated as per the study protocol design of the planned pediatric trial. Samples were quantified predose, and 2, 4, 8, and 24 h after dosing. Each subject's model-based $AUC_{0\text{-}24h}$ and $C_{max(0\text{-}24h)}$ were compared with the model-based adult PI for $AUC_{0\text{-}24h}$ and $C_{max(0\text{-}24h)}$, resulting from the same dosing regimen. Different cutoffs for the definition of successful was studied, corresponding to 20 to 22 out of 24 pediatric subjects in a trial being predicted to have $AUC_{0\text{-}24h}$ and $C_{max(0\text{-}24h)}$ being within the adult PI for $AUC_{0\text{-}24h}$ and $C_{max(0\text{-}24h)}$.

Hardware and software

Data processing and NONMEM runs were performed on an Intel Core i5-5300U CPU-based personal computer, running under Windows 10 Professional (64 bit), as well as on the Uppsala Multidisciplinary Center for Advanced Computational Science (UPPMAX) cluster (Unix, 304 nodes, 6080 cores, 2×10 cores/node, 274×128 GB, 30×256 GB Infiniband interconnect). The clinical trial simulations were performed in the nonlinear mixed effect modeling software NONMEM (version 7.4.3)[29] supplemented with the PsN toolkit, version 4.4.8,[30] using the GNU Fortran version 5.1.0 compiler. R statistical software was used for data management and analysis of the results.[31]

RESULTS

The explorations of the relationship between CL and BW normalized CL versus BW illustrated that the relationships are nonlinear. Notably, the BW normalized CL values versus BW showed that the trend is nonlinear with higher CL per kg of BW at lower BW, with most of the nonlinear trend being below BW of 14 kg, corresponding to the median BW for 2-year-old children in the NHANES database (Figure S1). Above 14 kg, the relationship is

approximately linear, which has been shown previously for FVIIa.[32]

The median (range) BW values in the simulated virtual populations (1000 children per age group 0.5, 1, 2, 4, 6, and 11 years) were 8 (6–10), 12 (8–16), 14 (11–20), 18 (14–35), 23 (16–41), and 45 (26–89) kg, respectively. For the plausible study design of 24 pediatric subjects that was simulated 1000 times for the probability of trial success (24 new pediatric subjects in each trial), the median and range of BW per age group (<2, 2 to <6, and 6 to 11 years) over all trials were 9.6 (range 3.3–16.2), 16.3 (10.4–37.7), and 31.8 (16.3–89.2) kg.

Exposure-matching clinical trial simulations to inform dose selection

The target adult matching range (95% PI for $AUC_{0\text{-}24h}$ and $C_{max0\text{-}24h}$), was derived from simulations following a single, two, or three 60 μg/kg doses, given in 3-h intervals. The matching ranges were 196–1611 h·ng/mL and 12–93 ng/mL, 375–2976 h·ng/mL and 22–179 ng/mL, and 536–4401 h·ng/mL and 34–269 ng/mL, for $AUC_{0\text{-}24h}$ and $C_{max0\text{-}24h}$, respectively.

For the 60 μg/kg dose level across all dosing intervals and age groups, the lower bound of the 95% PI (2.5th percentile) of predicted $AUC_{0\text{-}24h}$ was only slightly lower than the lower bound of the 95% PI in adults (Figure 1). For the 75 μg/kg, only the 2, 1, and 0.5-year-old age groups showed a slightly lower predicted $AUC_{0\text{-}24h}$ compared to the corresponding adult PI (Figure 1). In contrast to all other dose levels, the upper bound of the $AUC_{0\text{-}24h}$ 95% PI following the 60 μg/kg dose level did not exceed the upper limit of the target in any of the age groups and independent of number of doses (Figure 1). A similar pattern was seen for predicted $C_{max(0\text{-}24h)}$ across all age groups and dosing regimens. For a single dose, two doses or three doses given 3 h apart, the 60 μg/kg dose level had a lower bound of the 95% PI only slightly lower than the corresponding limit in adults in all age groups (Figure 2). The dose level that appeared most similar to the 60 μg/kg dose level in terms of exposure was 75 μg/kg. The 75 μg/kg dose level had upper ends of the 95% PI above the adult matching range in 11- and 6-year-old groups (Figure 2). Increasing the dose level to 75, 90, 105, or 120 μg/kg had a more pronounced effect on the upper end of the 95% PI as compared to the lower end (Figure 2).

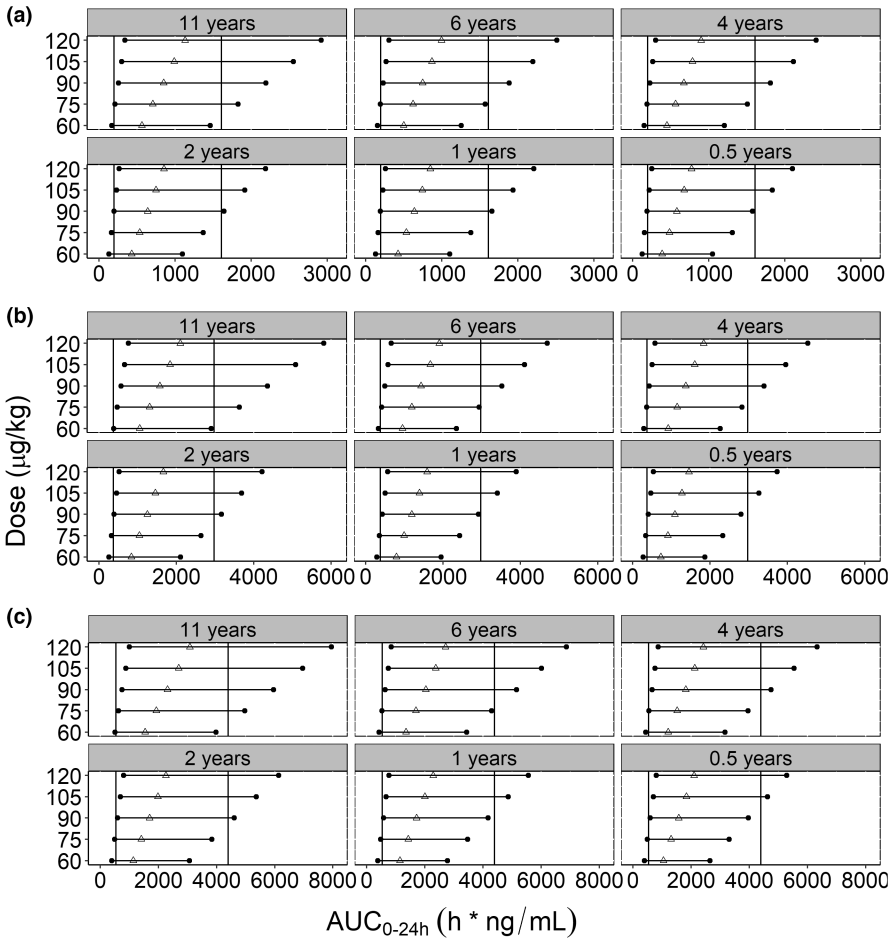


FIGURE 1 Predictions of area under the concentration curve over 24 h ($AUC_{0\text{-}24h}$) in the pediatric population for different age groups and dose levels given (a) as a single dose, (b) two doses 3 h apart, and (c) three doses 3 h apart. The vertical lines are the adult 95% prediction interval based on a 60 μg/kg dose level and can be viewed as the adult matching range.

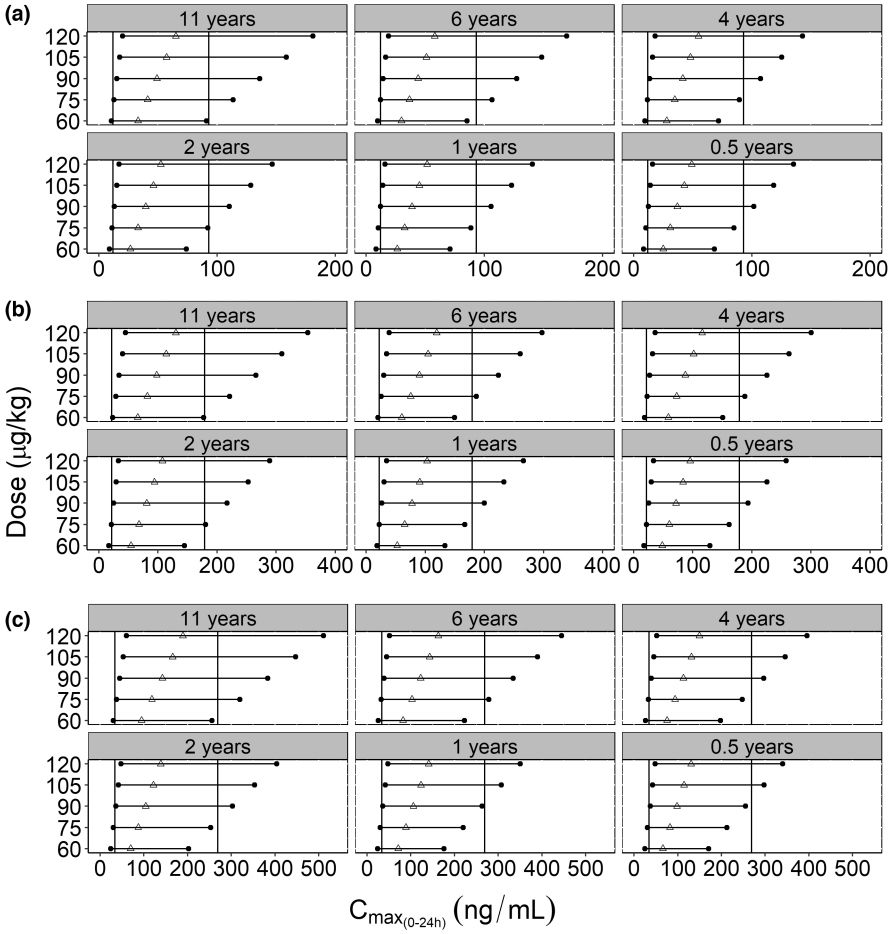


FIGURE 2 Predictions of maximum concentration over 24 h ($C_{max(0\text{-}24h)}$) in the pediatric population for different age groups and dose levels given (a) as a single dose, (b) two doses 3 h apart, and (c) three doses 3 h apart. The vertical lines are the adult 95% prediction interval based on a 60 µg/kg dose level and can be viewed as the adult matching range.

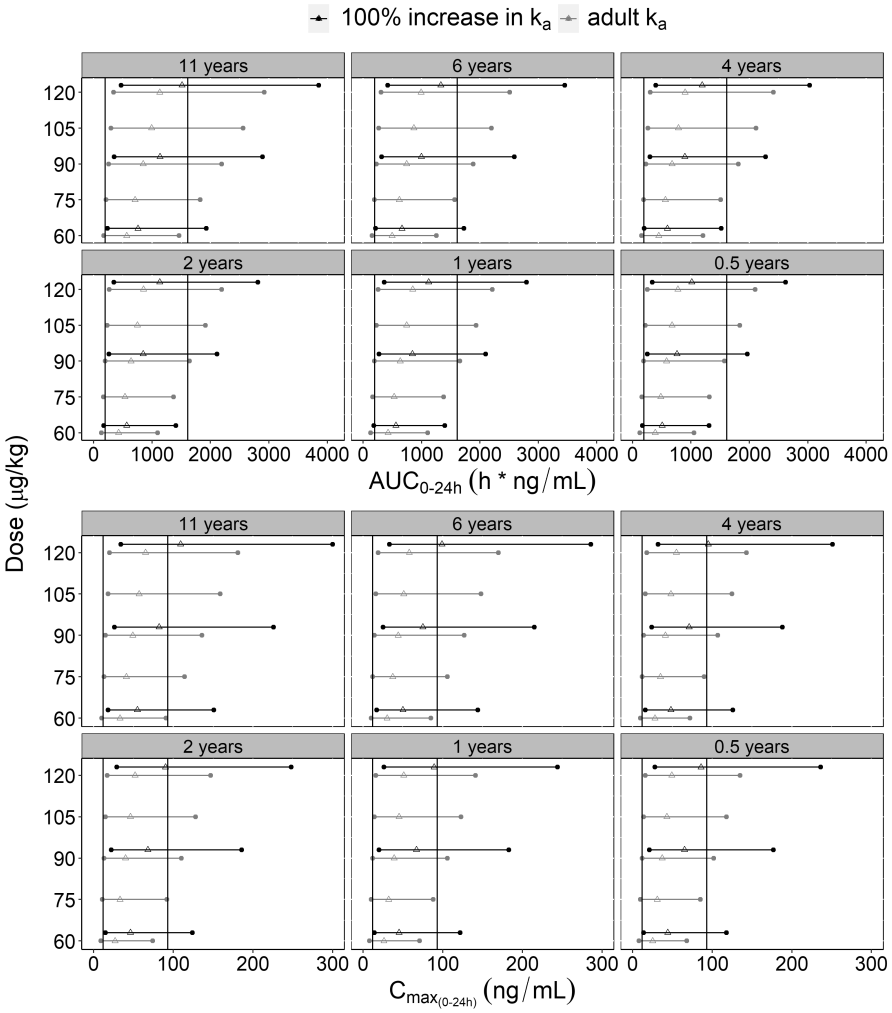
Sensitivity analysis

To study the impact on dose selection for a putative higher absorption rate in pediatric subjects compared to adults, a doubling of the absorption rate was studied. The 95% PI of $AUC_{0\text{-}24h}$ and $C_{max(0\text{-}24h)}$ assuming adult absorption rate or the doubled absorption rate, including the respective matching ranges, are shown in Figure 3. The simulated 95% PI of $AUC_{0\text{-}24h}$ remained similar to the matching range for 60 µg/kg in all age groups except the 11- and 6-year-old groups, where the upper bound of the interval was slightly above the matching range. For the two higher doses in which a doubled absorption rate was studied (90 and 120 µg/kg), all age groups were found to have the upper limit of the PI above the upper end of the adult matching range. The 95% PI of simulated $C_{max(0\text{-}24h)}$ had upper ends of the interval above the matching range in all age groups and dose levels, and was especially pronounced for the 4, 6, and 11-year-old age groups, and two highest dose levels of 90 and 120 µg/kg (Figure 3). In general, the hypothetical increase in absorption had a higher impact on the upper end of the PI. The median $AUC_{0\text{-}24h}$ following a single dose of 60 µg/kg increased by 31% and 34% for the 0.5 and 11-year-old group, respectively. For $C_{max(0\text{-}24h)}$, doubling the absorption constant increased the median by 76% and 67% for the 0.5 and 11-year-old groups, respectively, following a single 60 µg/kg dose.

The additional sensitivity analysis in which the exponent of CL was set to 0.75 for the 11- and 6-year-old groups, 0.9 for the 4-year-old group, and 1 for the 2, 1, and 0.5-year-old groups further supported the dose selection of 60 µg/kg. The assumed difference of the exponent in the 4, 2, 1, and 0.5-year-old groups pushed the 95% PI in greater agreement with the adult 95% PI for $AUC_{0\text{-}24h}$ and $C_{max(0\text{-}24h)}$ (Figures S2 and S3). The dose resulting in the closest agreement with 60 µg/kg was 75 µg/kg when using 0.75 as the CL exponent. However, with the ADE allometric approach, the 75 µg/kg dose level resulted in almost all age groups exceeding adult exposures for both $AUC_{0\text{-}24h}$ and $C_{max(0\text{-}24h)}$, further indicating the 60 µg/kg dose level to be appropriate in all age groups (Figures S2 and S3).

Probability of trial success

To study the probability of trial success with a proposed dose of 60 µg/kg in all age groups, including 24 pediatric subjects, 1000 clinical trials were simulated, and each individual's $AUC_{0\text{-}24h}$ and $C_{max(0\text{-}24h)}$ were compared with the adult matching range. The distribution of $AUC_{0\text{-}24h}$ and



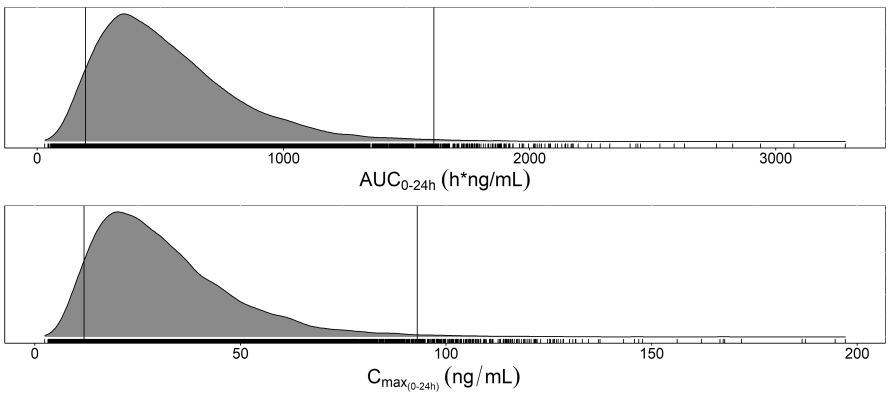


FIGURE 3 Predictions of area under the concentration curve over 24 h ($AUC_{0\text{-}24h}$) and maximum concentration over 24 h ($C_{max(0\text{-}24h)}$) in the pediatric population for different age groups and dose levels given as a single dose with the adult absorption rate (k_a) value (gray, lower) or doubled k_a (black, upper).

FIGURE 4 Distribution of area under the concentration curve over 24 h ($AUC_{0\text{-}24h}$) and maximum concentration over 24 h ($C_{max(0\text{-}24h)}$) after a single 60 µg/kg dose from 1000 clinical trials with 24 pediatric subjects in each trial ($n = 24{,}000$). The vertical black lines illustrate the 95% prediction interval from adults given the same dose and the ticks along the *x*-axis illustrate each $AUC_{0\text{-}24h}$ and $C_{max(0\text{-}24h)}$ value.

$C_{max(0\text{-}24h)}$ across all 1000 trials ($n = 24{,}000$ pediatric subjects) are shown in Figure 4, along with the 95% PI from adults resulting from the same dose level. Using criteria of 20 out of 24 pediatric subjects in a given trial to be within the 95% PI in adults for $AUC_{0\text{-}24h}$ and $C_{max(0\text{-}24h)}$, the probability of trial success was found to be 99% and 97% based on $AUC_{0\text{-}24h}$ or $C_{max(0\text{-}24h)}$. The corresponding probability of trial success for more stricter criteria of requiring 21 or 22 out of pediatric subjects to be within the target led to 98% and 89% based on $AUC_{0\text{-}24h}$ and 91% and 74% based on $C_{max(0\text{-}24h)}$.

DISCUSSION

This work was conducted to support potential phase III dose selection of s.c. MarzAA to treat acute bleeding episodes in pediatric subjects with HA/HB with inhibitors. In line with regulatory requirements, and to mitigate problems that arise in rare diseases such as small sample sizes, an exposure-matching strategy was outlined assuming that the underlying disease mechanism and the exposure-response relationship are similar between pediatric and adult patients.[33] These assumptions should be considered in light of a quantitative exposure-response relationship was not established for FVIIa. However, as dosing often is repeated, efficacious exposure levels will be reached and the bleeding event resolved following repeated dosing. As efficacy data become available in children, the assumptions can be evaluated and an exposure-response relationship can be established.

To make an informed decision for first-in-pediatric dose, clinical trial simulations were performed with different regimens, followed by sensitivity analysis covering a potential difference of absorption rate in children, as compared to what has been found in adults. In addition, a stratified exponent approach based on age was used in the dose selection simulations as a sensitivity analysis. A promising dose level for treatment of episodic bleeding (60 μg/kg) was taken forward and studied in a plausible clinical trial setting for probability of trial success, and was found likely to satisfy similarity to adult exposures. However, it is important to emphasize that confirmation of the exposure-matching strategy is needed in a PK run-in part of the phase III trial, prior to initiation of efficacy evaluations. After PK data in children has been obtained, the model can be updated and the simulations can be re-done to confirm or refine the pediatric doses. This approach would lead to a more adequate dose to be tested in the efficacy evaluations. A similar update can be performed when efficacy data have been generated in children to evaluate the exposure-response relationship. This pediatric development strategy is beneficial, as it negates the need for a dedicated separate PK study in children. This is particularly important in rare diseases where recruitment is often challenging.

Similar to previous reports,[32] the theoretical exploration of BW normalized CL relationship with BW showed a nonlinear relationship (Figure S1), with most of the nonlinearity below 14 kg. Higher clearance in children have been reported in the literature[34] and may be related to age-related differences in body composition, such as liver volume per kg BW.[35,36] In general, allometric scaling may be reliable for initial dose selection in children above 2 years of age for small molecules and have been observed to be useful for FVIII and FIX,[18,37] whereas maturation functions (for therapeutic proteins representing development of protein metabolism) are recommended for predictions below 2 years of age.[38] However, to our knowledge, no quantitative description on maturational effects describing change in protein metabolism has been reported for rFVIIa drugs and therefore uncertainty remains on change in CL in children below 2 years of age. In absence of data in children, the initial pediatric dose needs to be based on some relationships. Allometry with fixed exponents and an ADE approach has been shown to be useful for therapeutic proteins.[18,19] Although allometry with fixed exponents were considered useful for the initial dose selection, it is associated with uncertainty and confirmation/evaluation of the assumption can be done when data in children are available and the model can be updated. An alternative to using a fixed exponent of 0.75 is the ADE allometric approach that uses different exponents for different age groups, which can help mitigate the potential risk of overdosing subjects below 2 years of age.[17,19,21] The ADE model has previously demonstrated superiority over fixing the exponent to 0.75 for CL for small molecules[17,21] and for biologics.[19] It is important, however, to emphasize the potential uncertainty associated with the ADE method and that the exponents may be drug-specific (i.e., that other values per age group is more appropriate for MarzAA). This method was selected as an alternative to maturation factors for scaling as the latter is not available for MarzAA. The ADE allometric approach can be considered useful for first-in-pediatric dose-selection. When PK data in children are available following a PK run-in part, the recommended dose for efficacy assessments can be confirmed or reconsidered and the true nature of the allometric relationship can be explored with higher certainty.

To make an informed decision, the exposure in pediatric age groups were compared to the exposures arising from the selected phase III dose in adults (60 μg/kg). It was found that a dose level of 60 μg/kg given once, two times 3 h apart or three times 3 h apart resulted in $AUC_{0\text{-}24h}$ and $C_{max(0\text{-}24h)}$ distributions close to the adult matching range in all age groups. This indicates that a single 60 μg/kg dose has the potential to stop an acute bleeding event in pediatric patients. Previous simulations have shown that in the case of failure to stop an acute bleed in adults after a single 60 μg/kg dose, a second dose was predicted to give desirable rFVIIa levels above target in greater than 90% of adult patients.[23] Thus, whereas a single dose is promising and may be enough in many cases, a second dose can be administered after 3 h if the bleeding did not stop. For the lowest four age groups (0.5, 1, 2, and 4 years), a dose of 75 μg/kg was also found to be comparable with the adult matching ranges. However, when considering the ADE allometric approach (Figures S2 and S3) a dose of 60 μg/kg appeared to be more appropriate.

Recent evidence has suggested that most therapeutic proteins have higher absorption rates in pediatric populations due to increased extracellular fluid volume and higher perfusion rates. This has been confirmed for abatacept and tocilizumab s.c. administrations but also for intramuscular palivizumab.[26,27] As expected, a doubling of absorption rate for MarzAA increased $AUC_{0\text{-}24h}$ and $C_{max(0\text{-}24h)}$, with more pronounced effect on the latter. $AUC_{0\text{-}24h}$ remained within the adult matching range for the 60 μg/kg dose level except for the 11- and 6-year-old age groups, which had levels higher than the upper end of the 95% PI in adults. However, the consequences might be minor for these two groups as increase in absorption are in general expected to be more pronounced for newborns and infants in comparison to older children.[27] For $C_{max(0\text{-}24h)}$, the simulations showed that pediatric peak levels might exceed the upper limit of the adult matching range. As the most common adverse event is thrombotic events following usage of i.v. NovoSeven, s.c. administered formulations, such as MarzAA, have potential to mitigate the risk through a prolonged and more smooth exposure profile. Continuous infusions producing plasma levels up to 30 IU/mL have been used safely in patients with hemophilia.[39] A potential doubling of the absorption rate, which was considered as an extreme case, led to $C_{max(0\text{-}24h)}$ levels below 30 IU/mL (which is equivalent to 120 ng/mL of MarzAA considering at least 5-fold increase in potency compared to wt-rFVIIa)[9,23,40,41] in a vast majority of patients (Figure 3) with the 60 μg/kg dose level. The empirically selected doubling of absorption rate was considered an extreme case in this sensitivity analysis, and, as such, the difference in absorption between children and adults remains to be confirmed in a clinical setting. The simulations can be updated with respect to absorption rate and other potential differences prior to initialization of efficacy evaluations, based on data generated in a run-in PK study.

To verify the exposure matching strategy in a plausible trial design of 24 pediatric subjects, 1000 clinical trials were simulated. The total number of 24 pediatric subjects was considered reasonable due to difficulties in recruiting subjects with HA/HB with inhibitors, and have recently been justified with respect to efficacy in another pediatric program for an rFVIIa compound that was evaluated in a similar setup as planned for MarzAA.[42,43] For each trial, each pediatric patient $AUC_{0\text{-}24h}$ and $C_{max(0\text{-}24h)}$ was compared to the adult matching range. Allowing for three pediatric subjects to be outside of the adult matching range resulted in probability of trial success greater than 90% considering both $AUC_{0\text{-}24h}$ and $C_{max(0\text{-}24h)}$. Stricter criteria of 23 or 24 out of 24 children being within the adult matching range was not performed as allowing for two to four children to be outside of the adult exposure matching range was considered sufficient. The probability of trial success simulations is dependent on the sample size in each age group. Infants and newborns are expected to have a higher clearance per kg of BW thus potentially risk of underexposure. In this work, it was considered plausible to recruit two subjects less than 2 years of age. The small number of subjects in that group will impact the probability of trial success simulations. However, the simulations in large populations (Figures 1 and 2, 0.5- and 2-year-old age groups) showed potential for exposure matching to adults also in those age groups. Another factor expected to impact the probability of trial success simulations is the exponent of CL, which was set to 0.75 for all different cutoffs that defined a successful trial. However, as the simulations in large populations showed a greater agreement with adult exposures when using the ADE allometric approach, the result is expected to be similar for the probability of trial success.

In conclusion, this model-informed work supported a first-in-pediatric dose of 60 μg/kg by s.c. administration in a registrational phase III trial using one to three doses every 3 h as needed, in pediatric individuals with HA/HB with inhibitors. A run-in PK phase was agreed upon with regulators to confirm the dose, prior to initiation of efficacy evaluations, instead of a separate dedicated PK study in pediatrics. The work presented here shows how modeling and simulations coupled with an exposure matching strategy may be used in a rare disease setting to inform first-in-pediatric dose selection for a drug candidate that has not been studied in earlier pediatric trials.

AUTHOR CONTRIBUTIONS

A.F., R.C.vW., U.S.H.S., S.D., L.N., T.K., and G.E.B. wrote the manuscript. A.F., R.C.vW., U.S.H.S., S.D., L.N., T.K., and G.E.B. designed the research. A.F., R.C.vW., U.S.H.S., S.D., L.N., T.K., and G.E.B. performed the research. A.F., R.C.vW., U.S.H.S., S.D., L.N., T.K., and G.E.B. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

S.D., L.N., G.E.B., and T.K. are/were employees and shareholders of Catalyst Biosciences. All other authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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